Abstract View

LENTIVIRUS-MEDIATED EXPRESSION OF HUMAN APOLIPOPROTEIN E ALTERS BRAIN Aß BURDEN IN AN ISOFORM-DEPENDENT MANNER IN PDAPP MICE.

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A highly replicated genetic association between apolipoprotein E (apoE) polymorphisms and the risk to develop late-onset Alzheimer's disease (AD) has now been established. Individuals carrying one or two ε4 alleles develop AD at a younger age and have higher brain amyloid burden compared to individuals carrying two ε3 alleles. Moreover, genetic epidemiological studies suggest a protective role for the ε2 allele, which reduces the risk of AD. Both in vitro and in vivo studies suggest that apoE alters brain deposition and/or clearance of the amyloid ß-peptide (Aß), a 4-kD peptide which abnormally accumulates in brain to form amyloid-containing neuritic plaques in AD. In the present study, we have investigated whether lentivirus-mediated expression of the most common human apoE isoforms can alter brain Aß burden, neuropathology and behavior in a mouse model of AD. PDAPP mice with substantial brain Aß burden received bilateral hippocampal injections of lentivirus preparations containing GFP (control), apoE2, apoE3 or apoE4 constructs. Mice were then perfused 5 or 12 weeks post-injection and their brains processed for biochemical as well as histological analyses. Following lentivirus-mediated apoE2 expression a significant reduction of hippocampal Aß burden was measured with a specific Aß ELISA and by quantitative immunohistochemistry at both 5 and 12 weeks. Additionally, preliminary data suggests that lentivirus-mediated expression of apoE4 alters hippocampal Aß/amyloid burden in PDAPP mice lacking endogenous murine apoE. Our data demonstrate that human apoE can be efficiently delivered to the brain via lentiviral vectors and that apoE gene delivery alters Aß pathology in an isoform-dependent manner in a mouse model of AD.

Citation:
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